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- (54) Title: **AGENT FOR INHIBITING SYMMETRICAL PROTEINS, IN
PARTICULAR ENZYMES**

(57) Abstract

The invention concerns an agent for inhibiting symmetrical proteins, in particular enzymes, in particular for inhibiting the HIV protease, in the form of structurally symmetrical or almost symmetrically formed enzyme inhibitors which are characterized by the fact that the molecule of the enzyme inhibitors has the same symmetry as the enzyme molecule to be inhibited or partially or approximately the same symmetry, but in any event is sufficiently symmetrical to ensure inhibition.

Agent for the inhibition of symmetrical proteins, in particular of enzymes.

The discovery concerns an agent for the inhibition of symmetrical enzymes, in particular the inhibition of the HIV proteinase and/or protease, by means of structurally symmetrical or almost or partially symmetrically formed enzyme inhibitors.

An important consideration of medicine is the specific inhibition of foreign enzymes (from pathogenic bacteria or viruses) or of the body's own enzymes in pathological situations, because it makes possible a non-destructive therapy. The invention was the result of experiments to find such specific inhibitors for the immune deficiency disease AIDS (Acquired Immune Deficiency Syndrome). The experiments took place on the proteinase, referred to by the short name "protease," of HIV (Human Immunodeficiency Virus), a specific enzyme produced by the HI-virus which causes AIDS. This enzyme is responsible for the processing of the predecessor proteins. It splits off from them the finished virus

proteins from which the complete virus is assembled. A specific inhibition of the HIV protease should prevent the proliferation of the virus and cure the symptoms. The strategy of specific inhibition of protease for AIDS is particularly significant, since on the one hand, immunological inhibitory measures bring with the risk of destroying the remaining immune defenses of the body, and on the other hand, the therapy utilizing the presently known inhibitors of the reverse transcriptase of HIV (for example, AZT, FLT, Suramine), another virus specific enzyme, is limited by most severe side effects. Also treatment of AIDS based on other compounds (for example the polysulfated polysaccharides) has not yet been convincingly demonstrated or is associated with severe side effects.

There is an extensive literature on the HIV protease, of which the by way of example the following are cited:

- L. H. Pearl & W. R. Taylor, Nature (1987) 329, 351-354
- I. Katoh et al, Nature (1987) 329, 654-656
- C. Debouck et al., P.N.A.S. (1987) 84, 8903-8906
- P. L. Dracke et al., B.B.Res.Comm. (1988) 156, 297-303
- S.F.J. Le Grice et al., EMBO J. (1988) 7, 2547-2553
- M.C. Graves et al., P.N.A.S. (1988) 85, 2499-2453
- M. Kotler et al., P.N.A.S. (1988) 85, 4185-4189
- S. Billich et al., J.B.C. (1988) 263, 17905-17908
- S. Seelmeier et al., P.N.A.S. (1988) 85, 6612-6616

- E.P. Lillehoj et al., J. Fiol. (1988) 62, 3053-3058
L.E. Henderson et al., J. Virol. (1988) 62, 2587-2595
H.-G. Kräusslich et al., J. Virol. (1988) 62, 4393-4397
M. Miller et al., J. Mol. Biol. (1988) 204, 211-212

The purpose of the invention is to achieve a more effective influencing of proteases (through the associated proteins) in order, for example, to realize a more effective treatment of AIDS and other diseases in which enzymes are involved. In achieving this, a high degree of specificity and a favorable therapeutic index are of decisive importance.

This task is carried out through enzyme inhibitors the molecules of which are structurally of the same, approximately the same, or partially the same symmetry as the enzyme molecule which is to be inhibited.

Enzyme inhibitors of this kind are therefore customized in their symmetry with respect to the symmetry of the enzyme, essential to the progression of the disease, which is to be inhibited. The inhibitors are synthesized in a manner known as such and are then administered, also in usual pharmacological methods for example i.v. or orally. By means of this process, the inhibition of the enzyme through the compounds represents a useable treatment.

It was determined that structurally symmetrically formed (called "symmetrical" for brevity) enzyme inhibitors are particularly well suited to inhibit the proliferation of HI viruses by means of inhibition of the symmetrical virus coded proteases which consist of two identical half-molecules. It was further recognized that other symmetrical enzymes could also be inhibited in this manner. Symmetrical or partially symmetrical enzyme inhibitors are known (for example for a reverse transcriptase, the structure and symmetry of which was however not yet known). But the present operating principle of the matching of the symmetry of the enzyme and the symmetry of the enzyme inhibitor was not known. Symmetrical inhibitors based upon peptides, as far as is known, have not been previously been described and also could not have been anticipated, since the natural substrates of enzymes, including enzymes which are symmetrical, are never symmetrical. The invention is based on the recognition that in such reactions (bonding of unsymmetrical substrates to symmetrical enzymes, or the inhibition of symmetrically formed enzymes through unsymmetrical peptide inhibitors), either only one half of the peptide (the half that has a good fit) is responsible for the bonding and the other half has only an auxiliary function, or that neither side has an optimal fit but together they have sufficient affinity. In contrast, well fitted peptides and peptide derivatives (or other symmetrical organic chemical compounds) should be able to provide a stronger bonding (and likewise a stronger inhibitory effect) than unsymmetrical peptides.

It was further recognized that enzyme complexes consisting of sub-units - symmetrical as well as unsymmetrical - could be inhibited if the cohesion of the individual sub-units could be disturbed through appropriate compounds, so that either a complete or partial dissolution or a destabilization of the complex results, or the formation of the complex or the spatial structure or conformation which is appropriate for the enzymatic reaction is completely or partially prevented. This can also be achieved by providing peptides or peptide-like compounds or other organic chemical compounds which contain amino acid sequences or are derived from or related to such compounds which occur in the native enzymes and are responsible for the function of the necessary tertiary or quaternary structure.

This is particularly with respect to the active center of the enzyme complexes where even relatively minor disturbances of the structure can result in the enzyme becoming inactive. Therefore peptides with sequences of the peptide chains which form the active center or which stabilize it are particularly well suited to inhibit the activity of the enzyme by disturbing the structure preventing the formation of the correct spatial enzyme structure. It is not necessary that the compounds used for this purpose be symmetrical, but symmetrical enzymes are particularly effective because there are several identical bonding points and the effect therefore is multiplied according to the number of sub-units. This

principle also holds true for non-symmetrical proteins which are, however composed of combined sub-units.

The advantages are a very specific inhibition of proteins (enzymes or proteases), because the precise structural characteristics of the target protein are taken into consideration and the property of symmetry is exploited for a stronger bonding of the inhibitor due to the bonding area being at least doubled.

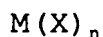
In the case of AIDS, as with other diseases, the high degree of specificity and bonding strength of the inhibitors allows a relatively non-destructive treatment. This is particularly important in the case of AIDS since a very non-destructive treatment is needed, because AIDS damages the immune system, and therefore the susceptibility of the body to all kinds of other diseases increases drastically. Additionally, particularly with AIDS, which can not be causally cured since the virus nuclear acids become integrally incorporated in to the genome, a life-long therapy is necessary and therefore a very non-destructive and specific treatment is necessary.

Such a substance is distinguished in particular by having a peptide or a peptide-like structure or another central organic chemical compound, which for the sake of simplicity shall be called M, on which residues X, Y, Z, U, R are bonded as side chains, which can be organic residues, in particular amino acids or derivatives of

amino acids or monosaccharides or derivatives of the same or residues of fatty acids or their derivatives, particularly peptides which are all identical or nearly identical and are symmetrical or approximately symmetrical in relation to the group H, so over all a symmetrical, approximately symmetrical, or partially symmetrical compound results. The term "Symmetry" is to be understood here in the usual sense of stereochemistry. Thus in the case of proteins it always refers to an axis of rotation.

In this way proteins, particularly enzymes, can be inhibited by means of such inhibitors if they have at least a local symmetry with respect to the inhibitable portion of the molecule. These are for example enzymes which consist in part or completely of the same sub-units, although they can have additional sub-units. In addition to HIV-proteases, about which this is known, there are also other viral proteins, membrane proteins, cytokines, restriction enzymes, and multi-enzyme complexes whose symmetry is either known or can be adequately determined.

The symmetrical inhibitors for the symmetrical proteins have the same symmetry as the proteins which are to be inhibited and consist, as mentioned, of a central group M and side arms, which for the sake of simplicity shall be designated here with the letter X. Thus a formula is obtained in the following form



in which the numerical index of the symmetry of the protein is "2," in the case of 2-fold axis, symmetry C_2 , for example.

As mentioned, the side arms can consist of amino acids, peptides or derivatives or other organic chemical compounds. However, peptides have the advantage among other things of being accessible by means of easy, partially automatic synthesis. In theory, however, fatty acids, carbohydrates, and even anorganic compounds are possible as side arms if they are suited to the particular enzyme. Utilization of peptides primarily with 2 to 4 amino acids per side arm is most preferable.

The two arms or the several arms must be symmetrical, approximately, or partially symmetrical to each other in the sense that the symmetry of the protein which is to be inhibited, for example, a 2-fold symmetry is repeated in the inhibitor. In the example of a dyad, it must therefore be possible to lead one side arm of the inhibitor over into the other by turning around a two-fold axis.

This can be accomplished for example in the following way:

- a) If the orientation of the peptide chain in the two halves is different, such that in one half the NH-CO-vector points to the center while in the other half it points out from the

center, then a counter balance must be created through the utilization of amino acids of opposite chirality (D instead of L or vice versa). The inhibitor created in this way is then approximately symmetrical with respect to the side chains, but in any case not to the peptide bonds. But this is ordinarily sufficient for the inhibitor to be adequately symmetrical to the enzyme to be inhibited.

- b) If not all amino acids or other residues of the inhibitors are symmetrical, but rather, for example, a tyrosine is completed on one side by a phenylalanine but the remaining amino acids are like and are complementary, a high level of inhibitory activity should be expected. Inhibitors of this type can even be more desirable with respect to solubility, ability to pass through a membrane, and similar characteristics. Physical-chemical parameters such as size, charge, hydrophility, and the like is determinative. Thus the inhibitor

Phe-Thr-Ile-M-Leu-Ser-Tyr

is more "symmetrical" with respect to the characteristics listed than

Ala-Arg-Gly-M-Gly-Asp-Ala (unequal charge, Arg/Asp),

or

Gly-Gly-Try-M-Gly-Gly-Gly (unequal size, Try/Gly),

since the difference, for example, between Thr on one side and Ser on the other side is smaller than between Arg and Asp or between Try and Gly.

For this reason, small deviations from the symmetry can in principle even be an advantage. It is only necessary that the increase in affinity based on optimal structural matching (through matching of symmetry) be just great enough for strong bonding.

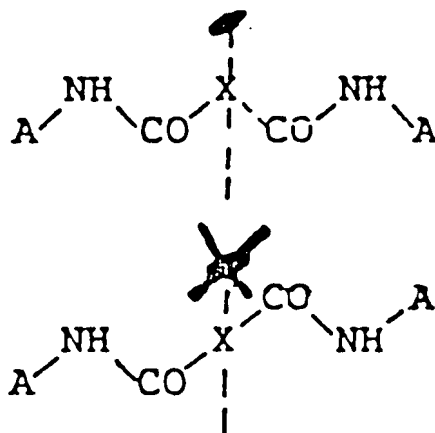
The central groups have the following functions:

- a) to transmit the symmetry of the protein to inhibitor
- b) to keep the side arms, which is responsible in part for a good bond, in the proper spacing and angle of bonding
- c) to contribute on its own account to a good bonding of the inhibitor and thus to the inhibition of the protein by means of a good fit with the protein, for example, with the active center of an enzyme.

The central groups do not necessarily have to be symmetrical themselves, for example if the side arms are largely responsible for the affinity. The central group can be chiral, for example statine. What is important is that the transmission of the orientation of the side arms and the proper separating spaces be optimal. But this is not a problem for the laboratory chemist with a knowledge of the symmetry or possibly even the precise structure of the enzyme. The size of the central groups can be different, as can be their chemical nature. Thus even inorganic groups such as -P(=O)OH- or even only one bond can serve as central group. A structural mimicry by the inhibitor of the substrate or

of a transitory condition of an enzymatic reaction can be important.

Central groups are unsuitable, if, although they do have the correct side chains (corresponding sequence and chirality of the amino acids) in the proper spacing, one arm is arranged wrong with respect to the direction of the axis of symmetry, for example if "up" and "down" are reversed.



The following examples illustrate partially or approximately symmetrical peptides which result in an inhibition of the HI-viruses in H9 cells.

Example 1

- A) H-(D)-Asn-(D)-Leu-(D)-Thr-Gly-OH
- B) t-BOC-L-Leu-NE-CH₂-CHOH-CH₂-COOH

reversal of the directional orientation of the amino acids, for example (D)-A-NHCO-(D)-B-NHCO-(D)-C-NHCO-(D)-D- instead of a natural substrate peptide with the formula (L)-A-COHN-(L)-C-COHN-(L)-D-. The pairs D and A or C and b should be symmetrical or should at least demonstrate a structural similarity (with respect to hydrophobicity, charge, size of the side chains, etc.).

EXAMPLE 3

Acetyl-(D)-Arg-(D)-Ala-(D)-Gln-(D)-Leu-NH-CO-CH(C₄H₉)-CO-(L)-Gln-(L)-Ala-(L)-Arg-NH₂

Acetyl-(L)-Arg-(L)-Ala-(L)-Asn-(L)-Leu-NH-CH₂-CH(C₃H₇)-CO-(D)-Asn-(D)-Gln-(D)-Leu-NH₂

Acetyl-(D)-Arg-(D)-Ala-(D)-Gln-NH-CH₂-CO-CH₂-CO-(L)-Gln-(L)-Ala-(L)-Arg-NH₂

Acetyl-(D)-Arg-(D)-Ala-(D)-Asn-Statin-(L)-Asn-(L)-Ala-(L)-Arg-NH₂

Acetyl-(L)-Arg-(L)-Ala-(L)-Gln-Statin-(D)-Gln-(D)-Ala-(D)-Arg-OH

Fluoracetyl-(L)-Arg-(L)-Ala-(L)-Asn-Statin-(D)-Asn-(D)-Ala-(D)-Arg-NH₂

Acetyl- (D) -Arg- (D) -Ala- (D) -Leu-Statin- (L) -Leu- (L) -Ala-
(L) -Arg-NH₂

Acetyl- (D) -Leu- (D) -Arg- (D) -Asn-NH-CH₂-CH (OH) -CH₂-CO-
(L) -Asn- (L) -Arg- (L) -Leu-NH₂

Part of the peptide chain in the compounds used can consist of residues of amino acids of one spatial configuration while the other half consist of amino acids of reversed configuration, such that a symmetrical or partially symmetrical overall compound results. As an example, this can be in accordance with the principle expressed in the formulas

(L) -C- (L) -B- (L) -A- (D) -A- (D) -B- (D) -C

or

(D) -C- (D) -B- (D) -A- (L) -A- (L) -B- (L) -C

with A, B, and C representing residues of amino acids. Care must be take, to insure that the principle discussed at the top of page 6 is adhered to through the insertion of an appropriate central group M (in the center).

Likewise, in the case of inhibition for proteases, the enzyme inhibition can be achieved the several means described below.

An enzyme inhibitor which has a non-cleavable bond rather than a cleavable peptide bond, as illustrated by Example 7 may be used.

- C) $\text{Cl-CH}_2\text{-CO-Gly-Ala-Phe-Pro-Ile-Ala-OH}$
- D) $\text{CH}_3\text{CO-Thr-Leu-Asn-NH-CH}_2\text{-CHOH-CH}_2\text{-NH-Asn-Leu-Thr-COCH}_3$
- E) $\text{Ala-Asp-Thr-B-Naphthylamid}$
- F) $\text{CH}_2\text{-(-CH}_2\text{CO-(D)-Asn-(D)-Leu-(D)-Thr-Gly-OH)}_2$

The compounds (a), (b), (c), and (d) were tested at molarities of 0.1uM to 1000uM. Infectiousness experiments were carried out as follows: a HIV-1 suspension containing 10^2 infective units was absorbed on 5×10^6 H9 cells in a volume of 1mm for a period of 2 hours at 4 °C. After this time period, 9ml of tissue culture medium containing the appropriate inhibitor concentration was added. Every day the medium was replaced with new medium plus inhibitor. Two control cultures without inhibitor were also tested. The purpose of one of the control cultures was to determine the normal level of virus replication. Also a culture with inhibitor without virus was tested, in order to determine whether these substances are cytotoxic for H9 cells. No cytotoxic effect was observed, as determined through staining the cells with trypan blue. The quantity of virus antigens produced by infected cells was measured daily for eight days by means of ELISA, with the HIV-1 antigen in the tissue culture medium being determined. After this period of time the cells were pelleted, were washed in medium without inhibitor, and were incubated further in medium without inhibitor. On days 7, 8, 9, and 12 the virus production was also measured by means of determination of reverse transcriptase of remaining amounts of the cell culture medium.

The results were a clear inhibition of HIV 1 replication as is shown in the attached tables 1 through 5 for compounds (a) through (d).

In the following examples, R and R' mean peptide residues, primarily with a maximum of 9 amino acids, most commonly with 2 to 4 amino acids, or other short organic chemical residues, for example $\text{CH}_3(\text{CH}_2)_n\text{CO}-$ where $n = 1$ through 10, $\text{CH}_3\text{CO}-$, $\text{H}-$, $-\text{NH}_2$, $-\text{NHR}$, $-\text{OR}$. X indicates small amino acid residues, such as Gly, Ala, Ser, or other small residues. A and B are amino acids or other organic residues. This holds true for all of the following examples if not otherwise indicated.

EXAMPLE 2

R-(D)-Ser-(D)-Gln-(D)-Leu-(D)-Phe-(D)-Ans-(D)-Gln-OR'

Acetyl-(D)-Asp-(D)-Leu-(D)-Phe-(D)-Leu-(D)-Ile-(D)-Lys-NH₂

Acetyl-(D)-Ala-(D)-Val-(D)-Pro-(D)-Phe-(D)-Asn-(D)-Arg-NH₂

Acetyl-(D)-Gln-(D)-Val-(D)-Ile-(D)-Pro-(D)-Tyr-(D)-Asn-
(D)-Gln-(D)-Arg-NH₂

When very similar to the substrate in other respects, such compounds can have a non-cleavable $-\text{HNCO}-$ bond or one that is cleavable only with difficulty in place of the cleavable $-\text{CONH}-$ peptide bond, thus with the direction reversed. An example would be the use of the retro-inverso principle with simultaneous

Compounds can be used in which two statin residues or two related compounds are attached in such a way to an asymmetrical central organic-chemical group that an overall spatial symmetry or approximate or partial symmetry with respect to the whole is brought about, as illustrated in Example 4.

Compounds can be used in which two peptides or peptide-like compounds with the same or nearly the same, mutually complementary sequence of amino acids and with the same configuration and/or chirality, but with reversed directionality are attached in such a way to a central organic-chemical group that overall a spacial symmetrical, or approximate or partial spatial symmetrical, total compound arises. This is illustrated in Example 7.

Furthermore, as illustrated in Example 8, compounds can be used in which two peptides or peptide-like compounds with the same sequence or nearly the same mutually complimentary sequence of amino acids with the same directionality of peptide bonds but with reversed chirality of the amino acids are attached in such a way to a central organic-chemical group having two different substituents that overall a total compound arises which is spatially symmetrical or approximately or partially symmetrical.

And finally, compounds can be used in which chemically reactive residues -- for example corresponding to the formulas

$\text{XCH}_2\text{-CO-}$, $\text{N}_2\text{CHCO-}$, $\text{NC-CH}_2\text{-CO-}$, $\text{RO}_2\text{C-}$, $\text{CH}_2=\text{CR-}$, $\text{RO}_n\text{S-}$, HS- , $\text{RO(H}_2\text{N=)C}^+\text{-}$
-- are attached in such a way to a symmetrical or approximately or partially symmetrical compound that the compounds of the target enzyme can be reversibly or irreversibly bonded. Here X signifies halogens, R is an ester residue with 1 to 12 carbon atoms, but preferably a C1-C3-residue, or a phenyl- or benzyl- residue and n + 1 to 3.

EXAMPLE 4

R-Statin-X-Statin-R'

$\text{CH}_3\text{CO-Statin-X-Statin-NH}_2$

Isovaleryl-Ser-Ser-Statin=Ala-Statin-NH₂

Acetyl-Ser-Statin-Gly-Statin-NH₂

Acetyl-Statin-Ala-Statin-NH₂

Fluoracetyl-Statin-Ala-Statin-NH₂

Acetyl-Statin-Ala-Statin-NH-CO-CH₂-CN

Additionally:

Combinations of (3S,4S)-, (3R,4R)-, (3R,5S)-, and (3S,4R)-Statin in the above manner or in similar manner.

Modification of R corresponding to the sequence of pepstatin A, the bonding sequences in typical substrates of HIV-proteases, etc.

In the compounds used, two statin residues or two related compounds are attached in such a way to an asymmetrical central organic-chemical group that an overall spatial symmetry or approximate or partial symmetry with respect to the whole arises.

EXAMPLE 5

R-Asp-Thr-Gly-R'

R-Asp-Ser-Gly-R'

R-A-Asp-Thr-Gly-B-R'

Acetyl-Ile-Asp-Thr-Gly-Ala-NH₂

Isovaleryl-Ile-Asp-Ser-Gly-Ala-NH-(CH₂)₃-CH₃

Acetyl-Asp-Thr-Gly-Ala-NH₂

Chloroacetyl-Asp-Thr-Gly-Asa-NH₂

Acetyl-Ile-Gly-Arg-Asn-NH₂

Acetyl-Ile-Gly-Gly-Arg-Asn-Ile-NH₂

The compounds used have the amino acid sequence Asp-Thr-Gly or Asp-Ser-Gly or related or similar amino acid sequences or organic-chemical residues which are structurally similar. Such sequences encourage or are responsible for the formation of a functional active center in the target enzyme from the same sub-units or from

corresponding parts of different sub-units. In this way, the compounds can limit the structure or the stability of the active center or can hinder the formation.

EXAMPLE 6

Acetyl-Thr-Leu-Trp-Gln-Arg-Pro-Leu-Val-NH₂

Fluoracetyl-Leu-Trp-Gln-Arg-Pro-Leu-NH₂

Isovaleryl-Trp-Gln-Arg-Pro-NH₂

H-Leu-Trp-Gln-Arg-Pro-NH₂, or similar compounds

In the case of HIV protease as the target enzyme, the compounds used contain the amino acid sequence Thr-Leu-Trp-Gln-Arg-Pro-Leu-Val or related or similar amino acid sequences or structurally similar organic-chemical residues or portions of them which are co-responsible for the association of sub-unites of HIV protease and the formation of or the cohesion of the functioning enzyme complex. Thus the compounds can retard the structure or stability of the enzyme complex or can reduce their enzymatic activity or can hinder their formation.

EXAMPLE 7

Acetyl-Arg-Leu-Asn-NH-(CH₂)₃-NH-Asn-Leu-Arg-Acetyl

Acetyl-Arg-Leu-Asn-NH-CH₂-O-CH₂-NH-Asn-Leu-Arg-Acetyl

Acetyl-Arg-Leu-Asn-NH-CH₂-CHOH-CH₂-NH-Asn-Leu-Arg-Acetyl

Acetyl-Arg-Leu-Asn-NH-CH₂-NH-CH₂-NCH₃-Asn-Leu-Arg-Acetyl

H- (D) -Leu- (D) -Leu- (D) -Asn-NH-CHP-CO-CHF-NH- (D) -Asn- (D) -Leu-
(D) -Arg-H

In the case of proteinases as the target enzyme, the enzyme inhibition is achieved by the compounds due to their having peptide bonds which are not cleavable rather than cleavable ones. By way of example, this can be in accordance with the following formulas:

-S-S-, -S-, -O-,

-CO-CHR-CH(OH)-CHR'-CO-, NR-NR'-,

-NH-CHR-CH(OH)-CHR'-NH-, -NH-CF₂-CO-CH₂-NH-,

-NH-CF₂-CO-CF₂-NH-, -CO-(CH₂)₃-CO-,

-NH-(CH₂)₃-NH-, -CO-H₂-CO-, N(OR)-, NR-,

-P(O)_nOH-, -CO-CHR-CO-,

-NH-CH₂-O-CH₂-NH-, -CO-CH₂-NR-CH₂-CO-,

-N(C₅H₁₁)-CF₂-CO-CF₂-N(C₄H₁₁)-,

-N(C₄H₉)-CH₂-CH(OH)-CH₂-N(C₄H₉)-,

-(2S, ₃S)-NH-CH(CH₂C₆H₁₁)-CH(OH)-CH₂-NR-,

or similar compounds. R and R' mean hydrogen or Aryl- or alkyl residues to C12 and n is 1 or 2.

In the compounds used, two peptides or peptide-like compounds with the same or nearly the same, mutually complementary sequence of amino acids and with the same configuration and/or chirality, but with reversed directionality are attached in such a way to a central organic-chemical group that overall a spacial symmetrical,

or approximate or partial spatial symmetrical, total compound arises. By way of example, this can be in accordance with the following formulas:

(L) -A-CONH- (L) -B-CONH- (L) -C-CONH-M-NHCO- (L) -C-NHCO-
(L) -B-NHCO- (L) -A

(L) -C-NHCO- (L) -B-NHCO- (L) -A-NHCO-M-CONH- (L) -A-CONH-
(L) -B-CONH- (L) -C

(L) -A-CONH- (L) -B-CONH- (L) -C-CONH-NHCO- (L) -C-NHCO-
(L) -B-NHCO- (L) -A

(L) -C-NHCO- (L) -B-NHCO- (L) -A-NHCO-CONH- (L) -A-CONH-
(L) -B-CONH- (L) -C

(L) -A-CONH- (D) -B-CONH- (L) -C-CONH-M-NHCO- (L) -C-NHCO-
(L) -B-NHCO- (L) -A

(L) -C-NHCO- (L) -B-NHCO- (L) -A-NHCO-M-CONH- (L) -A-CONH-
(L) -B-CONH- (D) -C

(L) -B-CONH- (L) -B-CONH- (L) -C-CONH-M-NHCO- (L) -C-NHCO-
(L) -B-NHCO- (L) -A

(L) -B-NHCO- (L) -A-NHCO-M-CONH- (L) -A-CONH- (L) -B-CONH- (L) -C.

A, B, and C represent amino acid residues and M represents a central organic-chemical group (see above for examples).

EXAMPLE 8

Acetyl-(L)-Arg-(L)-Leu-(L)-Asn-NH-(CH₂)₃-CO-(D)-Asn-
(D)-Leu-(D)-Arg-NH₂

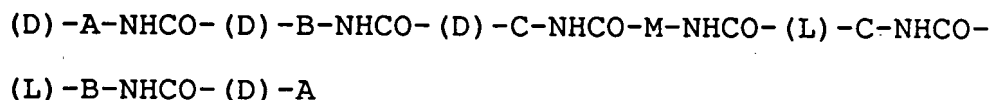
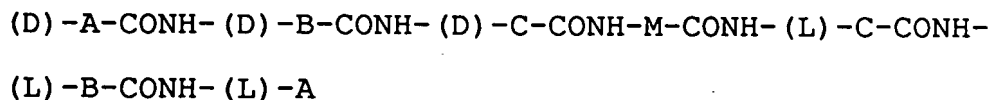
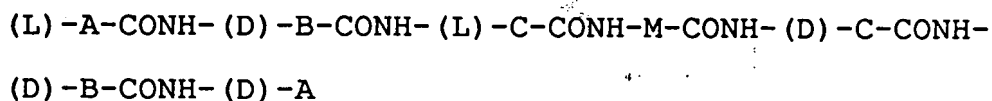
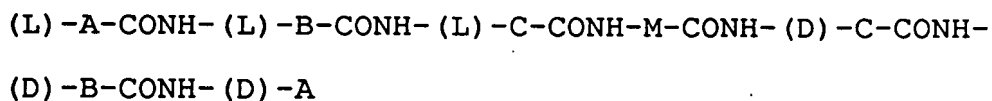
Acetyl-(L)-Arg-(L)-Leu-(L)-Asn-NH-CH₂-CHOH-CH₂-CO-
(D)-Asn-(D)-Leu-(D)-Arg-NH₂

H-(L)-Leu-(L)-Asn-NH-CH₂-CO-CF₂-CO-
(D)-Asn-(D)-Leu-(D)-Arg-NH₂

H-Val-Tyr-[CH₂-NH]-CH₂-[CH₂-NH]-(D)-Tyr-(D)-Val-OCH₃
(reduced -Tyr-Gly-D-Tyr-)

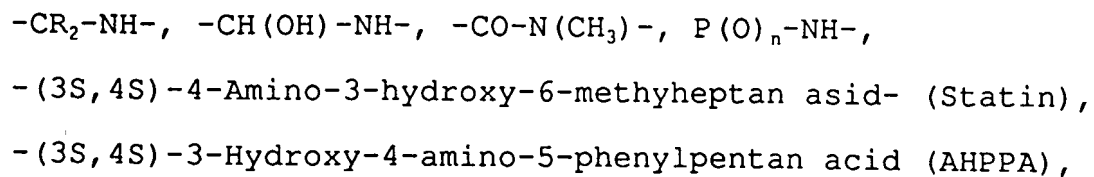
In addition to the possibilities given above in Example 7, compounds used here have two peptides or peptide-like compounds with the same sequence or nearly the same mutually complimentary sequence of amino acids with the same directionality of peptide bonds but with reversed chirality of the amino acids are attached in such a way to a central organic-chemical group having two different substituents such overall a total compound arises which is spatially symmetrical or approximately or partially symmetrical.

By way of example, this can be in accordance with the following formulas:



A, B, and C represent amino acid residues and represents a central group.

In the case of proteinases as the target enzyme, compounds used achieve the inhibition of the enzyme through having a non-cleavable peptide bond rather than cleavable ones. By way of example, they may be in accordance with the formulas



or similar compounds, whereby R and R' mean hydrogen or aryl- or alkyl residues up to C/12 and n is 1 or 2.

EXAMPLE 9

$\text{NH}_2\text{-Arg-Leu-Asn-CO-(CH}_2\text{)}_3\text{-CO-Asn-Leu-Lys-NH}_2$
 $\text{H}_2\text{N-(D)-Leu-(D)-Asn-CO-(CH}_2\text{)}_3\text{-CO-(D)-Asn-(D)-Ile-NH}_2$
 $\text{NH}_2\text{-Leu-Asn-CO-CH}_2\text{-NH-CH}_2\text{-CO-Asn-Leu-Arg-OR}$
 $\text{NH}_2\text{-Arg-Leu-Asn-CO-CH}_2\text{-CHOH-CH}_2\text{-CO-Asn-Leu-Arg-NH}_2$
 $\text{Acetyl-Arg-Leu-Asn-NH-CH}_2\text{-NH-CH}_2\text{-NH-Asn-Leu-Arg-Acetyl}$
 $\text{H-Leu-Leu-Asn-NH-CHF-CO-CHF-NH-Asn-Leu-Arg-H}$
 $\text{Acetyl-Arg-Leu-Asn-NH-CH}_2\text{-O-CH}_2\text{-NH-Asn-Leu-Arg-Acetyl}$
 $\text{Acetyl-Arg-Leu-Asn-NH-CH}_2\text{-CH(OH)-CH}_2\text{-NH-Asn-Leu-H}$
 $\text{H-(L)-Arg-(L)-Ile-(L)-Asn-NH-CH}_2\text{-CO-}$
 $\text{(D)-Gln-(D)-Leu-(D)-Arg-OH}$
 $\text{H-Ala-Ala-Statin-(D)-Val-(D)-Val-OCH}_3$

In addition to the possibilities indicated in the above two examples, the compounds used can have two peptides or peptide-like compounds with differing amino acid sequences, but with similar or complementary distribution of residues with the same electric charge or similar hydrophobicity or hydrophilicity or size of side chains or another physical-chemical characteristic incorporated into a central organic-chemical group in such a way that overall a spatially almost symmetrical or partially symmetrical total compound arises. For example, this could correspond to the formulas

(L) -C- (L) -A⁺-CONH-M-CONH- (D) -B⁺- (D) -C

(L) -C- (L) -A⁺-CONH-M-NHCO- (L) -B⁺- (L) -C

(L) -C- (L) -A⁺-CONH-M-CONH- (D) -B⁺- (D) -D

(L) -C- (L) -A⁺-CONH-M-CONH- (D) -B⁺- (L) -C

(L) -D- (L) -AX-CONH-M-NHCO- (L) -BX- (L) -C

(L) -C- (L) -AX-CONH-M-CONH- (D) -BX- (D) -C

(L) -C- (L) -AX-CONH-NHCO- (L) -BX- (L) -C

(L) -C- (L) -A⁺-HNCO-CONH- (D) -B⁺- (D) -D,

in which A⁺, B⁺ = two different amino acid residues with the same charge, M is a central organic-chemical group, and AX and BX are two different amino acids with comparably large hydrophobic or hydrophilic side chains.

In conclusion, a few examples for central groups (M), for side chains and for complete inhibitors will be cited.

Examples for central groups:

-NH-CH(OH)-CH(OH)-NH-, -O-, Statin,

-NH-CH(CH₂C₆H₁₁)-CH(OH)-CH₂-NH-,

-NH-CH(C₄H₉)-CO-CH(C₄H₉)-NH-,

-NH-CH₂-CH(OH)-CH₂-NH-,

(1S, 3S)-NH-CH(Cyclohexylmethyl)-CO-CH(Cyclohexylmethyl)-

NH-, 2-Alkylstatin, -CH₂-, Ethylenepoxid, Thiophen.

Examples for side chains:

Ac-Ser-Gln-Asn-Tyr-, H-His-Pro-His-Tyr-,
Ac-Arg-Ser-Gln-His-Cha-, H-Ala-Ala-

Examples for complete inhibitors:

tBoc-Arg-Ser-Gln-His-NR-CH₂-CH(OH)-CH₂-NR-His-Gln-Ser-Arg-
tBoc,

(R=-CH₂-CH(CH₃)₂, -CH-C₆H₁₁, etc.)

H-His-Pro-His-NH-CHR-CH(OH)-CH₂-NH-His-Pro-His-H

(R=-CH₂-C₆H₁₁ etc.)

Ac-His-Pro-His-NH-CHR-CH(OH)-CH₂-CO-NH-D-His-D-Gln-OCH₃

(R=-CH₂-C₆H₁₁ etc.)

Ac-Arg-Ser-Gln-Asn-

-NH-CH(CH₂C₆H₁₁)-CO-CHCH₂C₆H₁₁)-NH-

-Asn-Gln-Ser-Arg-Ac

(Central group: 1S,3S; in place of CO also -CH(OH)-, -CO-CO-,
-CH(OH)-CH(OH)-, Furan, Ethylenepoxid etc.)

tBoc-His-Pro-Phe-His-Leu-Statine-D-His-D-Phe-D-Pro-D-His-tBoc

A procedure for the inhibition of proteases, for example HIV protease by means of certain peptides consist, briefly outlined of:

1. determining the symmetry of the enzymes which are to be inhibited;
2. selecting the sequence of a good substrate or of an inhibiting peptide;
3. determining the center of the symmetry of the nearest amino acid;
4. linking a peptide, which will provide the bonding, to these amino acids by means of a chemical synthesis using a central group, such that an adequately symmetrical peptide is produced;
5. selecting the central group in 4. above in such a way that the corresponding amino acids are at the proper distance to the middle;
6. by means of computer aided molecular design check the goodness of the fit and determine the precise nature of the symmetry in the inhibitor;
7. monitor the inhibitory activity, in particular if the structural coordinates are not known. In this case optimize the sequence of the side arms and the structure of the central group through trial and error.

The chemical production of such compounds is known per se; also the administration of the compounds is known, so that the technician can rely here on the usual, familiar methodologies.

In conclusion, some preferred configuration with respect to inhibitory compounds are indicated.

Compounds which contain peptides or peptide-analogous structures or which consist of compounds derived from such structures. In this group the following symmetrical or partially symmetrical compounds are considered:

X-Y-Z-M-Z-Y-X, Z-M-Z, X-Y-Z-Z-Y-X, X-Y-Z-M-Z-Y',

X-U-Y-X-Z-Z-X-Y'-X, Z-Z-Y-R, R-U-X-Y-Z-M-Z, and also M alone,

whereby X, Y, Z, U, R are organic residues, particularly amino acids or derivatives, monosaccharide or derivatives, fatty acid residues or derivatives and M represents the central organic-chemical group and the two structures Y which are on either side of the central group are compounds similar in structure or in their physical-chemical characteristics. This can also apply or can instead apply to the other groups listed: X, A, U, or R. In the event of a good fit, a symmetrical group or almost symmetrical group M can be sufficient for the inhibition. An example of this is a dipeptide-analogue, as depicted at the top of page 14, for the group M from -NH- ... to ... -NH-.

The requirements for the bonding of the compound used to the target enzyme can, for example, be created by using in them typical splitting sequences or bonding sequences of the natural substrates or of structures related to them or structures of this type which have been modified in such a way that they will no

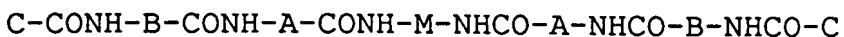
longer serve as a substrate for the target enzyme and act as inhibitors. The requirements for inhibition of the target enzymes can also be met in the compounds used by modifying the substrate or compounds similar to the substrate in such a way that they have areas which can no longer be changed enzymatically in place of those that can be, and therefore act as inhibitors.

A favored group of inhibiting compounds in the case of proteinases as the target enzymes have in place of the cleavable peptide bonds a dipeptide analogue with reduced peptide bonding or another similar compound with bonding which can not be cleaved and with similar length as a dipeptide and thus act as inhibitors for the target enzymes. In the case of proteinases as target enzymes, the compounds used can have in place of cleavable peptide bonding statin or a related or similar non cleavable bond with the same or similar length as a dipeptide. But also in the case of proteinases as target enzymes they can have in place of the cleavable peptide bonds a compound containing phosphorus which is not cleavable and has the same length or similar length as a dipeptide. An example of this is phosphon acid amide. Statin and similar dipeptide analogues in themselves represent nearly symmetrical compounds (symmetry close to -OH).

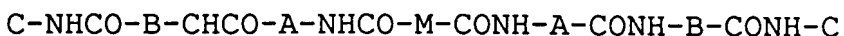
In the case of proteinases as the target enzyme, the place of the cleavable peptide bond can be spatially displaced in relation to the location of the cleavage points in a good substrate through

the introduction of a longer amino acid or another organic-chemical group. By this means the compound acts as an inhibitor for the target enzyme. For example, the location of the cleavable peptide bonds in the compounds used can be shifted in comparison with the location of the bond of a good substrate through the introduction of statin or of a related organic-chemical group or of another group.

In the compounds used, the symmetry or partial symmetry of the compounds can be achieved through the presence in the compounds of central organic-chemical groups which act as centers of the symmetry or of the approximate symmetry or by means of the compounds used having central organic-chemical groups with two identical substituents or which are equivalent in their structure, which can react with identical or partially identical peptides or peptide-like compounds in such a way that a symmetrical or partially symmetrical overall compound arises. By way of example, this could correspond to the formulas



or



whereby A, B, and C represent amino acid residues and M represents a central organic-chemical; group. The compounds used can have a symmetrical or approximately symmetrical central organic-chemical group with two identical organic substituents or substituents which are equivalent in their function, which correspond in length at

least to that of a dipeptide and which can react with peptides or peptide-like compounds in such a way that a symmetrical or approximately or partially symmetrical overall compound arises. In the event the formula-example listed first above (...-NH-M-NH-...) represents a good inhibitor, it is necessary in the second example (...CO-M-CO-...) for the chirality of the same amino acids used (A,B,C) to be reversed ("D" forms) in order to achieve a similarly good fit and thus inhibition.

The following formulas are examples of a central organic-chemical group with two unlike substituents, to which two like or approximately similar peptides or complementary peptides or peptide-like compounds are attached:

C-CONH-B-CONH-A-CONH-M-CONH-A-CONH-B-CONH-C

or

C-NHCO-B-NHCO-A-NHCO-M-NHCO-A-NHCO-B-NHCO-C,

whereby A, B, and C are amino acid residues and M is the central organic-chemical group. In general, the sequence order alone is not sufficient for the constitution of an adequately "symmetrical" inhibitor, as will be discussed below (see also page 6).

The compounds used can also have two statin residues or two correspondingly related compounds with or without intervening groups, such that overall a spatially symmetrical or approximately or partially symmetrical total compound arises, whereby the

compounds used can contain two statin residues with opposite configuration or two correspondingly related compounds with or without intervening groups. The compounds used can contain two statin residues or two correspondingly related compounds with or without intervening groups, whereby one of the statin residues is at the end, in order to guarantee the free turning of the bonds so that the assumption of a spatially symmetrical or approximately or partially symmetrical conformation of the total compound is facilitated.

If part of the peptide chains of the compounds consists of a single spatial configuration (for example, L-shape) - as is ordinarily the case - the other half must consist of amino acids of the obverse configuration, in order to produce an adequately symmetrical inhibitor. For this purpose the following examples are preferred:

(L)-C-(L)-B-(L)-A-(D)-A-(D)-B-(D)-C

or

(D)-C-(D)-B-(D)-A-(L)-A-(L)-B-(L)-C,

whereby A, B, and C represent amino acid residues.

In the compounds used a non-peptide residue can be bonded to a peptide or to a peptide-like compound in such a way that an approximately or partially symmetrical total compound arises, for example with respect to one or several physical-chemical

characteristics such as charge, hydrophilicity, hydrophobicity or size of the side chains or of the residue, or side chain or a non-peptide residue is so bonded in the compound used to a peptide or a peptide-like compound or a peptide with a central organic-chemical group, for example corresponding to the formulas B-A-M-A-R or R-B-A-M-A or R-C-B-A-B-A or B-A-M-R,

whereby A, B, C, and D represent amino acid residues, M represents a central organic-chemical group and R represents an organic residue, in such a way that overall a total compound arises which is spatially approximately or partially symmetrical. This can be, for example, with respect to one or several physical-chemical characteristics such as charge, hydrophilicity, hydrophobicity or size of the side chain or of the residue.

Chemically reactive residues can be bonded to a symmetrical or partially or approximately symmetrical peptide or peptide-like compound in such a way that the compounds of the target enzyme can be bonded reversibly or irreversibly. By way of example, such chemically reactive residues can correspond to the formulas XCH_2CO- , N_2CHCO- , $NC-CH_2-CO-$, RO_2C- , $CH_2=CR-$, RO_nS- , $HS-$, $RO(H_2N=C)^+$. Again, n is the number 1 or 2 and R is an ordinary ester residue as indicated earlier.

The compounds used can also contain amino acid sequences of the enzymes or proteins which are co-responsible for the association of its sub-unites or partial structures, or for the

stability or structural arrangement of the functioning enzymes and proteins. Or they can have related or similar amino acid sequences of structurally similar organic-chemical residues such that the compounds can disturb the structure or stability of the enzymes or proteins or can disturb their enzymatic activity or their function or can change their formation. The compounds used can contain amino acid sequences or related or similar amino acid sequences or structurally similar organic residues of the HIV protease which are responsible for the association of the sub-units of the enzyme and for the formation or cohesion of the functioning enzyme complex in such a way that the compounds can limit the structure or the stability of the enzyme complexes or can reduce their activity or can prevent their formation.

The compounds used can preferably contain amino acid sequences

Try-Lys-Pro-Lys-Met-Ile-Gly-Gly-Ile-Gly-

Gly-Phe-Ile-Lys-Val-Arg; Gln-Ile-Leu-Ile-Glu-Cys;

Val-Gly-Pro-Thr-Pro-Val-Asn; Ile-Gly-Arg-Asn;

Ala-Gly-Arg-Asn-Leu-Leu-Thr-Gln-Ile or related or similar amino acid sequences or structurally similar organic residues or parts of them, which are responsible in part for the association of the sub-units or the HIV protease and the formation or the cohesion of the functioning enzyme complex in such a way that the compounds can limit the structure or the stability of the enzyme complexes or can reduce their activity as enzymes or can prevent their formation.

Thus by using stable organic-chemical compounds in this way, it is possible to inhibit the structure and/or the effect of enzymes which have a certain degree symmetry in that they consist of like or unlike sub-units, particularly of enzymes of pathogenic bacteria or viruses or of the body's own enzymes in pathological circumstances. This can serve as therapy if the compounds used contain amino acid sequences of structurally unsymmetrical complex target enzymes or related or similar amino acid sequences or structurally similar organic-chemical residues which are co-responsible for the association of the sub-unites of the enzymes and the formation and cohesion of the functioning enzyme complexes, so that the compounds limit or prevent the formation or the cohesion or the stability of the enzyme complexes and their activity.

1
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Reverse Transcriptase Determination (epm/ml)

Day post infection	7	8	9	12.
HIV Control 1	12401	23708	18921	165540
HIV Control 2	4183	30094	13680	168620
A 1000 µM	1529	2121	1550	104660
100 µM	5378	6407	12893	142240
10 µM	4615	5381	12517	117910
1 µM	4041	7460	9502	163130
0,1 µM	3929	6914	14455	137470
B 1000 µM	3441	3159	5503	149020
100 µM	4033	4418	6575	125290
10 µM	4614	4188	7187	164920
1 µM	6105	3006	8474	92020
0,1 µM	2099	3091	6180	106830

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Day post infection	no inhibitor		
	7	8	9
HIV Control 1	12401	23708	18921
HIV Control 2	4183	30054	13680
C 1000 μ M	7646	4308	5343
100 μ M	3838	6370	8860
10 μ M	5358	4398	8823
1 μ M	4575	3198	4186
0,1 μ M	5561	2314	7477
D 1000 μ M - Not tested	4393	2663	3022
100 μ M	4112	5411	2914
10 μ M	6777	2058	2227
1 μ M	5550	3844	2304
0,1 μ M			

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35 30 25 20 15 10 5 1

Day post infection	7	8	no inhibitor	
HIV Control 1	12401	23708	18921	165540
HIV Control 2	4183	30094	13680	168620
16 1000 μ M	3344	5760	9748	151010
100 μ M	3099	3709	10344	97040
10 μ M	4537	5825	4340	153830
1 μ M	3155	1663	6595	201520
0,1 μ M	5487	982	2994	149330
17 1000 μ M	4859	5194	3874	129790
100 μ M	3770	5958	6656	129730
10 μ M	4854	8069	-	164570
1 μ M	2955	7606	3925	122840
0,1 μ M	3328	5959	4279	93946

Conclusion: All substances tested showed a significant inhibitory effect on HIV-1 replication as measured by total antigen production or by reverse transcriptase measurement of released virus. This effect was reversible as virus production quickly returned to control levels after removal of inhibitor from infected cells.

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Results: HIV-1 antigen production as measured in antigen capture ELISA, values
are o. D. H 9 cells readings.

Day post Infection	no inhibitor											
	1	2	3	4	5	6	7	8	9	12		
HIV Control 1	0,075	0,059	0,068	0,059	0,080	0,182	0,811	0,748	1,052	1,017		
HIV Control 2	0,074	0,062	0,063	0,059	0,053	0,115	0,498	0,698	1,338	1,048		
A 1000 μM	0,087	0,058	0,073	0,054	0,056	0,102	0,286	0,597	0,899	1,054		
100 μM	0,068	0,064	0,065	0,053	0,057	0,070	0,361	0,374	0,915	1,013		
10 μM	0,061	0,075	0,069	0,044	0,064	0,140	0,256	0,499	0,727	1,003		
1 μM	0,064	0,060	0,075	0,057	0,053	0,136	0,213	0,394	0,694	1,065		
0,1 μM	0,060	0,066	0,062	0,055	0,058	0,181	0,363	0,478	0,737	1,037		
B 1000 μM	0,076	0,068	0,050	0,050	0,063	0,075	0,279	0,577	0,811	1,050		
100 μM	0,068	0,070	0,063	0,052	0,052	0,099	0,359	0,260	0,890	0,960		
10 μM	0,063	0,060	0,059	0,047	0,055	0,087	0,303	0,342	0,645	1,038		
1 μM	0,063	0,060	0,061	0,050	0,052	0,105	0,186	0,237	0,745	0,970		
0,1 μM	0,061	0,063	0,039	0,063	0,055	0,149	0,389	0,232	0,700	1,047		
C 1000 μM	0,071	0,053	0,061	0,057	0,123	0,096	0,415	0,778	1,019	1,000		
100 μM	0,064	0,056	0,062	0,053	0,061	0,100	0,265	0,296	0,787	0,940		
10 μM	0,069	0,048	0,066	0,064	0,049	0,099	0,228	0,292	0,643	1,040		
1 μM	0,061	0,054	0,060	0,050	0,051	0,133	0,267	0,239	0,808	1,042		
0,1 μM	0,062	0,069	0,055	0,052	0,054	0,105	0,276	0,336	0,588	1,010		

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Day post infection	1	2	3	4	5	6	7	8	9	12
D 1000 μM - not tested										
100 μM	0,067	0,032	0,064	0,060	0,059	0,079	0,175	0,369	0,412	0,278
10 μM	0,068	0,066	0,072	0,060	0,059	0,081	0,218	0,368	0,886	0,975
1 μM	0,064	0,057	0,055	0,044	0,053	0,108	0,244	0,465	0,854	1,031
0,1 μM	0,057	0,055	0,051	0,054	0,057	0,134	0,380	0,366	0,906	0,996
16 1000 μM	0,076	0,055	0,062	0,051	0,065	0,086	0,354	0,379	0,905	0,975
100 μM	0,065	0,063	0,058	0,052	0,062	0,084	0,258	0,268	0,626	1,050
10 μM	0,065	0,066	0,064	0,050	0,058	0,107	0,308	0,308	0,738	1,059
1 μM	0,066	0,056	0,069	0,055	0,059	0,124	0,458	0,464	0,907	1,028
0,1 μM	0,058	0,064	0,045	0,043	0,053	0,115	0,266	0,525	0,870	1,002
17 1000 μM	0,065	0,063	0,042	0,048	0,049	0,094	0,397	0,584	0,989	1,002
100 μM	0,064	0,059	0,069	0,056	0,056	0,100	0,407	0,547	0,924	1,060
10 μM	0,065	0,026	0,062	0,061	0,059	0,127	0,336	0,439	-	1,001
1 μM	0,067	0,061	0,068	0,051	0,058	0,149	0,354	0,367	0,891	1,020
0,1 μM	0,060	0,057	0,063	0,046	0,050	0,121	0,464	0,434	0,984	1,066

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Patent Claims

1. Agent for the inhibition of symmetrical proteins, particularly enzymes, particularly for the inhibition of HIV protease, in the form of structurally symmetrical or almost symmetrically formed enzyme inhibitors which are characterized by the fact that these enzyme inhibitors are such that their molecule, in relation to the enzyme which is to be inhibited, is structurally of the same symmetry or partially or approximately (but adequate in order to serve as an inhibitor) symmetrical.
2. Agent per Claim 1, characterized by the fact that the inhibitors are organic-chemical compounds, particularly peptides or have peptide-like structure and exhibit a central organic-chemical group M on which organic residues are bonded as side arms, particularly amino acids or derivatives of amino acids, monosaccharides or their derivatives or residues of fatty acids or their derivatives, particularly peptides, which in each case are like or approximately like and in relation to the Group M are symmetrical or approximately symmetrical.
3. Agent per Claim 1 or 2, characterized by the fact that the inhibitor compounds for the inhibition of proteinases have non-cleavable rather than cleavable peptide bonds.

4. Agent per Claim 3, characterized by the fact that the inhibitor compounds, otherwise having a structure very similar to the substrate, have
5. Agent per one or several of the above claims, characterized by the fact that the inhibitory compounds have central-organic groups feature two organic substituents, identical or equivalent in their function, which can react with two identical or partially identical peptides or with peptide-like compounds or with fatty acids to C₁₂ in such a way that a symmetrical or partially symmetrical total compound arises.
6. Agent per one or several of the above claims, characterized by the fact that two like or approximately like or complementary peptides or peptide-like compounds are bonded in the inhibitory compounds used to a central organic-chemical group with two unlike substituents in such a way that a spatially symmetrical or approximately symmetrical total compound arises.
7. Agent per one or several of the above claims, characterized by the fact that one part of the peptide chain in the inhibitory compounds used consists of amino acid residues of one spatial configuration while the other half consist of amino acids of the reverse configuration in such a way that a symmetrical or approximately or partially symmetrical total compound arises.

8. Agent per one or several of the above claims, characterized by the fact that the inhibitory compounds used in the case of HIV proteases contain the amino acid sequence Asp-Thr-Gly- or Asp-Ser-Gly or related or similar amino acid sequences or structurally similar organic-chemical residues which contribute to or are responsible in the target enzyme for the formation of a functional center of activity out of like or complementary parts of different sub-unit of complex enzymes in such a way that the compounds can limit the structure or the stability of the active center or can prevent the formation of the active enzyme.
9. Agent per one or several of the above claims, characterized by the fact that the inhibitory compounds in the case of HIV proteases contain the amino acid sequences Ile-Gly-Arg-Asn, Trp-Lys-Pro-Lys-Met-Ile-Gly-Gly-Ile-Gly-Gly-Phe-Ile-Lys-Val-Arg; Gln-Ile-Leu-Ile-Glu-Cys; Val-Gly-Pro-Thr-Pro-Val-Asn; Ile-Gly-Arg-Asn; Ala-Gly-Arg-Asn-Leu-Leu-Thr-Gln-Ile or related or similar amino acid sequences or structurally similar organic-chemical residues which contribute to or are responsible for the formation in the target enzyme of a functional active center of like or complementary parts of different sub-units of the complex enzymes in such a way that the compounds can limit the

structure or the stability of the active center or can prevent the formation of the active enzyme.
